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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/079,949
Filing Date: February 19, 2002
Appellant(s): ZANDI ET AL.

Antoinette Konski
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/5/10 appealing from the Office action mailed 9/2/09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

2, 5-7, 17-19, 21-23, and 42

(4) Status of Amendments After Final

The examiner agrees with the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

Appellants summary of the claimed subject matter of the application is substantially correct but includes several statements (all of the first two paragraphs on page 7 except for the first sentence thereof) which are in fact part of appellants

argument and not simply a summary of the claimed subject matter. These statements are not proper within this section of the appeal brief and will be addressed within the Response to arguments section.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner agrees with the appellant's statement of the grounds of rejection to be reviewed on appeal however, the examiner does not agree with appellants characterization of the Office's basis for the rejection. The Office's basis for this rejection will be fully set forth by the Office within this Examiner's Answer. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

F. Traincard et al. "Evidence for the presence of an NF-kappaB signal transduction system in Dictyostelium discoideum", J. Cell Science 112: 3529-3535. (Oct. 1999).

Epinat, J. et al. "Reconstitution of the NF- B System in Saccharomyces cerevisiae for Isolation of Effectors by Phenotype Modulation", Yeast 16:599-612. (1997).

D.M. Rothwarf et al. "IKK-gamma is an essential regulatory subunit of the IκB kinase complex". Nature. 395:297-300 (1998).

L. Ling et al. "NF-KB-inducing kinase activates IKK-α by phosphorylation of Ser-176" Proc. Natl. Acad. Sci. USA 95:3792-3797 (March 1998).

6,864,355 May et al. 3-2005

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 2, 5-7, 17-19, and 21-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Rothwarf et al. in view of Traincard et al. and Epinat et al.

Rothwarf et al. teach the coexpression of human IKKα, IKKβ and IKKγ genes in a eukaryotic host by inserting the genes encoding each subunit fused to a tag (HA or FLAG) into a mammalian expression vector (which includes the constitutively active β-actin promoter, growing the host cell, lysing the host cell, and immuno-precipitating the IKK complexes (see Figure 3). Rothwarf et al. further teach the production of an IKK complex including a mutant IKKγ subunit (i.e., an N-terminally truncated IKKγ, see Figure 6). Rothwarf et al. teach the importance of phosphorylation of the IKK complex for its kinase activity, teach that unstimulated cells producing the IKK complex still

have a basal level of kinase activity and further teach that the IKK complex can be phosphorylated *in vitro* by the NIK and MEKK1 proteins to produce an active complex. The only difference in the methods taught by Rothwarf et al. to the methods of the instant claims is that in the instant claims the expression host used is yeast.

Traincard et al. teach that within eukaryotic organisms, no homologs of any of member of the NF-κB signaling system (clearly disclosed as including Rel/NF-κB subunit genes, IκB subunit genes and IKK genes) has been found within the genomes of *C. elegans* or *Saccharomyces cerevisiae* both of which were fully sequenced genomes at the time of publication of Traincard et al.

Epinat et al. teach that yeast is a convenient host for the reconstitution of the NF-κB system since it does not contain any endogenous NF-κB activity (see page 603) and that the reconstituted system provides an easy assay for testing stimuli or specific proteins that are postulated to be involved in NF-κB signaling (see page 609). Epinat et al. further suggest that yeast lack any endogenous IKK activity (see Figure 4 and page 609) and teach expression vectors for the recombinant expression of genes involved in the NF-κB signaling pathway in yeast cells under the control of both constitutive promoters such as the *ADH1* promoter and inducible promoters such as the *GAL1* promoter.

The yeast expression vectors comprise selection markers such as the *URA3* or *LEU2* genes.

As the IKK complex is well known to be the part of the NF-κB signaling pathway responsible for IκB phosphorylation and as both Traincard et al. and Epinat et al. clearly suggest that yeast lack any endogenous IKK activity (as Traincard et al. teach that no IKK homologous genes were found in the yeast genome and Epinat et al. showed that an expressed IκB protein could not be phosphorylated in yeast even under similar stimuli to those known to induce IκB phosphorylation in mammals) and as yeast are well known in the art to be the workhorse organism for the expression of eukaryotic proteins of interest, it would have been obvious to one of ordinary skill in the art to reconstitute the IKK complex in a yeast host cells by expressing the IKK subunit genes of Rothwarf et al. in yeast using any known yeast expression vector or yeast expression vectors as taught by Epinat et al. One of ordinary skill in the art would understand that use of expression vectors such as those of Epinat et al. that include selection markers would include the growth of the yeast in selective media within which only yeast transformed with the desired vectors would grow. One of skill in the art would reasonably expect that coexpression of the three subunits together in yeast would produce a complex that would have the

basal level of kinase activity demonstrated by the unstimulated cells of Rothwarf et al. and even if this in fact proved not to be the case a skilled artisan would have clearly expected that active complex could be produced by lysing the yeast following expression and addition of exogenous NIK or MEKK1 to the lysate and then separating the active IKK complex or coexpressing NIK or MEKK1 in the yeast host as Rothwarf et al. clearly teach that these proteins activate the IKK complex *in vitro*. Note all of applicants claims use the term "comprising" and thus additional steps such as suggested are not excluded from the claims. While Rothwarf et al. do not teach where within the IKK complex the activating phosphorylation by NIK occurs, Ling et al. (the reference directly cited by Rothwarf et al. in support of the statement that the IKK complex can be phosphorylated by the NIK and MEKK1 proteins to produce an active complex) directly show that ***in vitro*** NIK phosphorylates IKK-α on Ser176 i.e., within the T-loop of IKK-α and shows that NIK also phosphorylates IKK-β (although to a lesser extent than it does IKK-α) See particularly page 3793 of Ling et al. Ling et al. do not specifically show that the phosphorylation of IKK-β is at Ser177 but this is the homologous residue in IKK-β to Ser 176 of IKK-α and thus a skilled artisan would expect this is the residue

phosphorylated in IKK-β and activation of the IKK complex in vitro by NIK would met the limitations recited in claim 42.

(10) Response to Argument

Appellants state that the claimed invention is based on the unexpected finding that IKK-γ regulates autophosphorylation of IKK-β leading to self-activation of the IKK complex. However, this was not unexpected as it was known in the art at the time of the invention (see for example column 25, lines 3-5 of US Patent 6,864,355 having priority to 5/22/00). Furthermore, even if this were an unexpected finding, the methods recited in the claims do not rely on this unexpected result to provide a biologically functional and activated IKK complex as they clearly use the transitional phrase "comprising" and thus do not exclude additional steps to activate recombinantly expressed IKK complex by methods which clearly were known in the art at the time of the invention. Applicants claims are drawn to making a functional and activated IKK complex NOT to methods of autophosphorylating IKK-β. Phoshorylation of IKK-β *in vitro* with NIK will produce an IKK complex structurally and functionally identical to the IKK complex produced by autophosphorylation (i.e., having Ser 177 of IKK-β phosphorylated). This method of activating the IKK complex was

taught by the prior art and is not excluded from appellants claims.

Appellants argue that it was believed as of the effective filing date of the present application, that activation of the IKK complex requires the TNF-α and NF-κB signaling pathways, such as proteins that activate NIK or MEKK1, and NEMO. First it should be noted that NEMO is simply another name for IKK-γ (see US Patent 6,864,355, column 7, lines 47-49) and thus applicants statement in fact acknowledges that it was known in the art that IKK-γ was involved in activation of the IKK complex. Furthermore, contrary to appellants assertion, the lack of the TNF-α and NF-κB signaling pathways in yeast would not have led a skilled artisan to believe that an activated IKK complex could not be produced by expressing nucleic acids encoding the IKK complex proteins in yeast as a skilled artisan would have reasonably expected that if the complex produced by simple coexpression was not fully activated that it could be activated *in vitro* with NIK and/or MEKK1. Doing this is within the scope of appellants claims. Appellants further state that the Office's statement that Rothwarf et al. teaches that the IKK complex can be activated *in vitro* in the absence of any cellular context further implies that activation of IKK by NIK and MEKK1 does not require the presence of the TNF-α and NF-κB signaling

pathways. The examiner for the most part agrees with this for at least NIK. Ling et al. showed activation of IKK activity in a reaction preformed in a test tube including IKK-α or IKK-β and NIK only (see figure 1 of Ling et al.) There are NO cells within this reaction, thus it is clearly an *in vitro* reaction and clearly shows that ALL that is necessary for activation of IKK-α and IKK-β is the additional presence of NIK. As such clearly the TNF-α and NF-κB signaling pathways are not necessary for activation to occur.

Appellants argue that the *in vitro* experiments in Rothwarf et al. (presumably Ling et al. was intended) were not carried out in the absence of any cellular context as the NIK and IKK proteins were first expressed in 293 cells (a human cell line) and then isolated from cells. The examiner agrees that this is true. However when the examiner stated "in the absence of any cellular context" she was speaking only of the activation reaction itself and NOT to the preparation of the components of the reaction. While human cells were used to prepare the IKK and NIK proteins used, the cells were removed prior to the use of the proteins. There are NO cells present during the activation reaction. Even though human cells were used to prepare the NIK protein the activation reaction is clearly an *in vitro* reaction with NO cells (and thus no TNF-α and NF-κB

signaling pathways) present yet the NIK did activate the IKK proteins. Clearly a skilled artisan would expect that this identical activation reaction could be used to activate IKK proteins which were expressed in yeast cells also. Furthermore, since there is NO indication that the 293 cells used for production of the NIK were in fact grown under conditions that activate the TNF-α and NF-κB signaling pathways, (i.e., under conditions in which an otherwise inactive NIK might have potentially been altered to produce an activated form), a skilled artisan would also reasonably expect that overexpression of NIK within the yeast cell which also was producing the IKK subunits would also result in an activated IKK complex. This coexpression of IKKα, IKKβ, IKKγ and NIK genes within yeast is also within the scope of applicants claims. Appellants state that Ling teaches that NIK becomes activated before phosphorylating IKK (citing page 3797 of Ling et al.) and therefore suggests that NIK would not be able to activate IKK without first being activated in the human cells by components of the TNF-α and NF-κB signaling pathways. However, appellants are taking the indicated portion of Ling et al. out of context. On page 3797 Ling et al. is describing the knowledge of how the TNF-α and NF-κB signaling pathways function *in vivo* and NOT what is necessary for NIK to activate IKK *in vitro*. Page 3793

described the preparation of the NIK used in the experiments of Figure 1 of Ling. Nothing in this description indicates that the 293 cells were grown in the presence of TNF-α or any other known activator of the TNF-α and NF-κB signaling pathways yet the NIK produced WAS functional *in vitro* in the experiments of Figure 1 to activate IKK activity. Furthermore, even if the art indicated that "activation" of NIK was absolutely required (which it clearly does not), given the prior art a skilled artisan would understand that the IKK subunits could be expressed in yeast cells, the yeast cells lysed, NIK which had been prepared in human cells added to the lysate (i.e., activated NIK) and the IKK complex isolated. Such a method is clearly suggested by the prior art and within the scope of appellants claims.

Appellants argue that the prior art teaches that activation of IKK by NIK requires IKK to be in a condition suitable for activation, specifically arguing that US patent 6,864,355 teaches that in the absence of NEMO (i.e., IKK-γ), IKK is phophorylated at a serine-rich region of the C-terminus of IKKβ making it refractory to NIK activation. However, appellants have misrepresented the statements of the patent. The patent does not state that in the absence of NEMO, IKK is refractory to

NIK activation but that in the absence of NEMO, IKK-β becomes auto-phoshorylated, basally active and refractory to TNF-α induced signals. Furthermore, the experiments of Ling et al. make it abundantly clear that appellants statement is clearly not true as the experiments of Ling et al, using NIK to activate IKK were all done in the absence of NEMO (i.e., IKK-γ) and even if the statement were true it is noted that the rejection clearly suggests using NIK to activate IKK complexes which include NEMO.

Appellants next go on (see bottom of page 13 - page 14 of appellants Brief) to discuss Rothwarf et al.'s statement that MEKK1 can be used to activate IKK *in vitro* also. The examiner agrees that the evidence with regard to MEKK1 is less clear and thus will not further discuss MEKK1 as it is not necessary to maintenance of the rejection, since the evidence is clear that NIK can be used as suggested.

Appellants argue that the rejection does not teach preparation of an autophosphorylated and activated IKK as prescribed by claim 42. However, the rejection clearly does suggest methods that would produce an IKK complex identical in structure (i.e., phosphorylated at Ser177 of the IKK-β T-loop) to that claimed by methods which include all recited steps of appellants claim. Although the rejection suggests the inclusion

of a step not actually recited in appellants claim (i.e., incubation with NIK or coexpression of NIK), this additional step is not excluded from any of appellants claims (including claim 42) as all claims recite the transitional phrase "comprising" which clearly allows the inclusion of additional steps. The examiner did not in the Final rejection of 9/2/09, specifically comment on claim 42, in isolation from the other claims as the limitations of this claim are met by the cited references in the same fashion as for the previous claims. The office Action did point out that the art makes it clear that the phosphorylation produced by NIK is at the site recited in claim 42 (see page 6 of the office Action). The new claim merely added a recitation of the specific phosphorylation which is necessarily present when the IKK complex is activated. Whether this phosphorylation is produced by IKK-β (i.e., autophosphorylation) or by NIK (i.e., a heterologous kinase), the IKK complex produced is structurally identical and meets the limitation recited in claim 42.

Appellants also not that the Office previously cited US Pate 6,684,355. However, this patent was not cited to reject the claims but merely to show that an assertion made by appellants was incorrect. Appellants had asserted that they were the first to disclose that the IKKγ subunit regulates the

autophosphorylation of the IKK complex. The examiner merely cited the patent to show that this was not the case as the patent clearly discloses this also. Furthermore appellants state that the Office alleged that the patent discloses that IKK-β is autophosphorylated at a serine-rich region of the C-terminus. However, no such assertion was ever made by the Office. The examiner agrees that the patent does teach that the C-terminal serine-rich region is one site of autophosphorylation of IKK-β, but the patent also clearly teaches that there are other sites of autophosphorylation in the remainder of the protein and it is these sites that are responsible for the activation only in response to inflammatory stimuli.

Finally appellants argue that the Office has failed to consider or at least comment on the additional limitations of the invention recited in the dependent claims. However, this is simply not true. Each of the limitations of the dependent claims were directly shown to be disclosed by one of the cited references. Briefly the limitations of claims 5-7, 18, 19, and 21-23 are taught by Rothwarf et al. and discussed within the description of the teachings of Rothwarf et al. and the limitations of claims 7, 17, and 21 are taught by Epinat et al. as discussed with the description of the teachings thereof and in the conclusion to the rejection. It is not necessary (and

would be an enormous waste of time and effort) to separately discuss each dependent claim where as here the limitations of the dependent claims are in fact taught by the cited references applied to the independent claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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